Seizure 21 (2012) 496–500

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Valproate sodium enhances body weight gain in patients with childhood epilepsy: A pathogenic mechanisms and open-label clinical trial of behavior therapy

Hideaki Kanemura [a,*], Fumikazu Sano [a], Yu-ichi Maeda [a], Kanji Sugita [a], Masao Aihara [b]

[a] Department of Pediatrics, Faculty of Medicine, University of Yamanashi, Japan
[b] Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Japan

ARTICLE INFO

Article history:
Received 19 March 2012
Received in revised form 1 May 2012
Accepted 6 May 2012

Keywords:
Valproate sodium (VPA)
Weight gain
Body mass index (BMI)
Obesity
Hyperinsulinemia
Behavior therapy

ABSTRACT

Objectives: Excessive weight gain associated with valproate sodium (VPA) may predispose patients with epilepsy to other health problems such as insulin resistance. The purpose of this study was to examine the changes in body weight and several biochemical parameters in children receiving VPA treatment. The effects of behavior therapy for epileptic children with VPA-induced weight gain are discussed.
Methods: Fifteen patients newly diagnosed with epilepsy were included in the study. The following parameters were measured: body weight, body mass index (BMI), serum glucose, serum insulin, serum VPA concentration and serum free carnitine. In addition, behavior therapy was introduced at the initiation of VPA therapy, and lasted at least for 2 years.
Results: After 6 months of follow-up, there were eight (53%) patients in whom weight gain was demonstrated. Significant increases in the serum insulin level and the insulin/glucose ratio were observed in the weight gain group ($p < 0.01$). All patients with significant weight gain showed increased appetite. However, BMI stopped increasing with intensive behavior therapy.
Conclusions: These findings suggest that an increase in serum insulin and insulin/glucose levels may cause weight gain, possibly by stimulating appetite, and that weight changes seem to be reversible with intensive behavior therapy without discontinuation of VPA.

1. Introduction

Valproate sodium (VPA) is a broad-spectrum anticonvulsant. VPA is not a sedative and it is associated with fewer cognitive or behavioral effects than other drugs such as phenobarbital.[1] On the other hand, VPA causes numerous side effects.[2] Patients with chronic epilepsy treated with VPA did not self-report any improvement in health-related quality of life.[3] Moreover, use of VPA in patients with epilepsy is associated with an increase in body weight that can interfere with treatment compliance.

Weight gain is a well-known adverse effect of VPA treatment, occurring in 40% of children.[4] Weight gain is the most common reason for patients to discontinue VPA treatment.[5–7] In a recent study, 38% of VPA-treated patients gained more than 10% of their body weight compared with 8% of patients treated with lamotrigine.[8] Further, weight gain associated with VPA seems to be appetite-related and not metabolic.[9] Although there has been recent interest in weight gain accompanying VPA therapy, the pathogenic mechanisms of this adverse effect remain unclear. In the study by Isojarvi et al., hyperandrogenism and polycystic ovaries were associated with weight gain, elevated fasting serum insulin levels, and serum low insulin-like growth factor-binding protein 1 (IGFBP-1) levels in women taking VPA for epilepsy.[10] These findings suggest that the weight gain can be progressive and is associated with hyperinsulinemia and low serum IGFBP-1 levels, which may lead to hyperandrogenism and polycystic ovaries. Thus, hyperinsulinemia may cause weight gain in patients taking VPA.

Many adverse health effects generally associated with adult obesity are now being seen in obese adolescents.[11,12] Behavior therapy is a psychological treatment based on the theory that the problem in question is maintained by certain dysfunctional cognitions and beliefs.[13,14] Basic components of behavior therapy are changing a child's eating habits, providing a moderate exercise program, implementing self-regulation skills and providing parental and peer support.[15] Excessive weight (e.g., obesity) is a complex interplay of environmental, social, economic, and behavioral factors, acting on the background of genetic susceptibility. Therefore, weight-control interventions are multifaceted and excessive weight or weight gain not simply treatable with behavior therapy. However, successful weight management may be possible without strict diet prescriptions.[16,17]

* Corresponding author at: Department of Pediatrics, Faculty of Medicine, University of Yamanashi, 1110 Chuo, Yamanashi 409-3898, Japan.
Tel.: +81 55 273 9606; fax: +81 55 273 6745.
E-mail address: ykimu@yamanashi.ac.jp (H. Kanemura).

1059-1311/$ – see front matter © 2012 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.seizure.2012.05.001

The purpose of this study was to examine the changes in body weight and several biochemical and endocrine parameters in older children and adolescents receiving VPA treatment. In addition, the effect of behavior therapy on VPA-induced weight gain is discussed.

2. Patients and methods

Fifteen patients (5 males and 10 females, mean age 11.1 years, range 7–16 years of age) newly diagnosed with epilepsy and for whom VPA was considered the most suitable treatment[18] were included in the study after informed parental consent was obtained. Patients were referred to the University of Yamanashi Hospital and its satellite hospitals between April 1, 2003 and March 31, 2005. Seven patients had idiopathic generalized epilepsy, and eight patients had idiopathic partial epilepsy with secondary generalization. Brain magnetic resonance imaging or computed tomographic scans were interpreted as normal. The average daily dose of VPA was 17.4 mg/kg (range, 13.6–23.1 mg/kg). No patients required other anticonvulsants in addition to VPA.

Participants were included if their weight and height were documented at the initiation of VPA treatment and if they returned for at least one follow-up visit during which their weight and height were re-measured. Those who were followed up for fewer than 3 months or who discontinued VPA treatment within 3 months of initiation, were excluded. Patients were also excluded if they received concurrent medication known to affect weight, such as antipsychotic agents, or stimulants.

The main screening assessments included seizure frequency, vital signs, physical and neurologic examinations, medical history, and standard clinical laboratory tests. Weight and height measurements were recorded at the initiation of VPA therapy and at all scheduled visits. Body mass index (BMI) was calculated at each of these points by dividing the weight in kilograms by the square of the height in meters. National growth chart findings based on data collected in a survey of Japanese children were used to obtain the mean body weight for height. The BMI category was defined as underweight, <18.5, appropriate, 18.5–21.5, potentially overweight, 21.5–25.0 and overweight, >25.0. Patients with a BMI increase exceeding 1.0 per 3 months were categorized in the weight gain group. In addition, we asked participants about appetite using the question "Has your appetite increased or decreased since starting the treatment?"

A blood sample was obtained between 8:30 and 9:00 am after an overnight fast and before breakfast. Weight and height were measured at the same time. The following parameters were measured using commercially available radioimmunoassay kits: serum glucose, serum insulin, serum VPA concentration, serum-free carnitine, triiodothyronine, thyroxine, thyroid-stimulating hormone, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

Potential predictors of BMI category at follow-up and BMI difference, including age at initiation of VPA, gender, VPA dose per weight (average maintenance dose, highest dose used), and average serum level, were recorded. The assessment was performed every 3 months.

The behavior therapy intervention was carried out by a pediatric neurologist trained in behavior therapy. Oral instruction for avoidance of weight gain was introduced to all patients at the initiation of VPA therapy. Our oral instructions for avoiding weight gain included the evidence that weight gain may cause metabolic and psychological problems. Further, programed behavior therapy was introduced to the weight-gainers at 6 months after VPA initiation. The intervention was conducted through work with both the children and their parents. The program of behavior therapy was based on lifestyle modification using a simple checklist.[19] Asayama et al. previously reported that the majority of the boys and nearly half of the girls participating in behavior therapy for longer than 200 days grew out of their obesity.[20] The behavior strategies consisted of several instructions as follows: (1) children and their families were instructed to regularly to eat three meals and one afternoon snack daily, avoiding intake of extra snacks, juices, oily (greasy) food additives, sugar and candies, and to drink no more than 200 ml of milk; (2) reduced caloric intake was not prescribed but patients were advised to observe the recommended daily allowance of food energy for each age and sex set by the Ministry of Education, Science and Culture of Japan; (3) children were instructed to play video or computer games for no more than 1 h a day; and (4) each child (or family) kept a checklist to evaluate (yes or no) whether they observed the seven recommendations (three meals and a snack, no night eating, video game limitations and doing their chores, etc.) on a daily basis. They reported their checklist scores (max. 7 points $\times$ 7 days per week) once every 3 months. We instructed the family on these points repeatedly at each visit (every 3 months). In this treatment program, diet was not restricted and fixed exercise regimes were not prescribed. Therefore, weight gain or excess were essentially intended to be ameliorated by life style modification with a modest change in body weight.[19] There was no other psychoeducational component to the intervention. The duration of behavior therapy was 15 min per session. The sessions were delivered as part of the routine epilepsy visit every 3 months. The behavior therapy was intensified as a result of participant or parental feedback from the checklist. The maximum-minimum frequency and duration of sessions was every 2–3 months and 15–30 min per session, respectively. The behavior therapy intervention lasted for at least two years.

We collected other data every 3 months in addition to the family's report of their adherence to recommendations. We assessed whether patients report their appetite as increased or decreased via the "appetite increased" question from the participants' reports. All data are presented as means for each group measure. The BMI difference for the two groups and the comparison between the two groups of patients was performed using ANOVA and Dunnett's test when appropriate. For statistical analysis, a p-value <0.05 was defined as statistically significant.

3. Results

We followed all patients from the beginning of therapy for at least two years. In the six months after the first observation, there were eight (53%) patients in whom weight gain was demonstrated (defined as an increase of BMI >1.0 in 3 months). However, no patients remained in the weight gain group at the end of the follow-up. Therefore, we subdivided the patients into two groups according to their BMI halfway through behavior therapy. Behavior therapy lasted for at least two years. Patient data are summarized in Table 1. There were no significant differences in body weight and BMI at VPA initiation between the weight gain ($n = 8$; mean age, 11.9 years; age range, 8–16 years: male:female = 0:8) and no weight gain groups ($n = 7$; mean age, 10.1 years; age range, 7–13 years; male:female = 5:2). However, the difference in BMI became significant during the course of the study ($p < 0.01$). Therefore, this subdivision was appropriate. We observed excellent seizure control with complete disappearance of seizures after 2 months of therapy in all patients in both groups. Thus, the severity and frequency of seizures were similar in the two groups. All patients remained seizure free until the end of the study. No patients required additional anticonvulsant medication during the study.

The mean BMI was 19.1 at initiation of VPA therapy for the entire sample (S.D., 2.4; range, 15.8–22.9). At onset, six (40.0%) subjects were in the underweight range, seven (46.7%) were in the

Table 1
Patient data.

Characteristics	Weight gain group ($n=8$)					No weight gain group ($n=7$)				
	First evaluation	After 3 months	After 6 months	After 1 year	After 2 years	First evaluation	After 3 months	After 6 months	After 1 year	After 2 years
BMI (kg/m^2)	20.03	21.19	22.09	20.75	20.08	17.94	17.96	17.77	17.86	17.83
Serum glucose (mg/dl)	84.75	89.13	93.13	89.25	87	84.57	85.71	88	86.57	86
Serum insulin (μU/ml)	11.28	15	16.83	14.48	13.28	10.39	10.56	10.56	10.44	10.59
Serum insulin to glucose ratio	0.133	0.169	0.181	0.163	0.153	0.123	0.123	0.12	0.121	0.123
Serum VPA concentration (μg/ml)	n.d.	65.55	64.18	66.93	68.4	n.d.	69.81	69.91	69.49	69.7
Serum carnitine (μmol/l)	44.75	43.38	44.75	44.38	44.08	40.21	41.74	42.01	41.57	42.13

BMI, body mass index; VPA, valproate sodium; n.d., not done.

appropriate weight range, and two (13.3%) were potentially overweight. The mean final BMI at follow-up was 19.0 (S.D., 4.2; range, 16.1–22.5), with seven (46.7%) in the underweight range, five (33.3%) in the appropriate weight range and three (20.0%) in the potentially overweight range. Children in overweight group at baseline were more likely to put on weight than children of normal weight or underweight children.

Weight change throughout the study during the drug treatment phase is depicted in Fig. 1. A significant increase in BMI was observed within 6 months after initiation of treatment in the weight gain group (Fig. 2). Weight gain occurred only in females, with significant differences between genders. Serum glucose, serum insulin, serum insulin to glucose ratio, VPA concentration, and serum carnitine are shown in Table 1. A significant increase in the insulin concentration was observed in the weight gain group ($p < 0.01$) (Fig. 3a). Glucose levels did not change significantly in either group. No correlation between alterations in glucose levels and weight gain was evident. The insulin/glucose ratio increased significantly in the weight gain group ($p < 0.01$) (Fig. 3b). All patients with marked weight gain showed increased appetite. Once behavior therapy had been intensified, however, the appetite decreased subjectively. In addition, both discontinuation of body weight increase and BMI decrease were seen after six months of intense behavior therapy (Figs. 1 and 2). Checklist scores were also increased (improved) after behavior therapy intensification (mean score 29.0 points/week before behavior therapy to 40.8 points/week 1 year after behavior therapy initiation). At the end of the study (year 2), BMI showed no significant change from levels measured before the initiation of treatment in both groups.

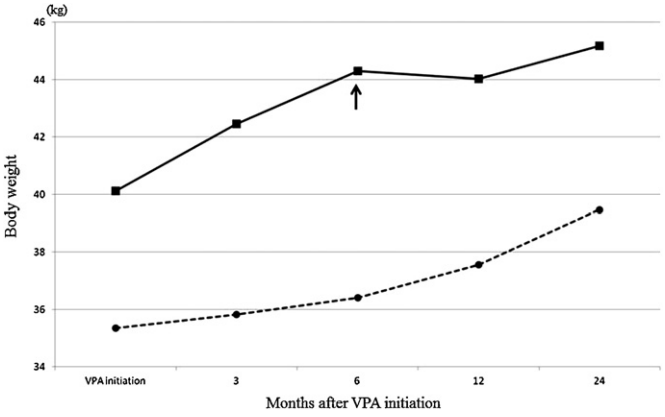

Fig. 1. Serial changes in mean body weight in patients after initiation of treatment with VPA. Body weight in the weight gain group increased within 6 months after initiation of treatment. By contrast, body weight increase was gentle in the no weight gain group. Closed squares with solid lines indicate the weight gain group. Closed circles with dotted lines indicate the no weight gain group. Arrow indicates the onset of intensive behavior therapy.

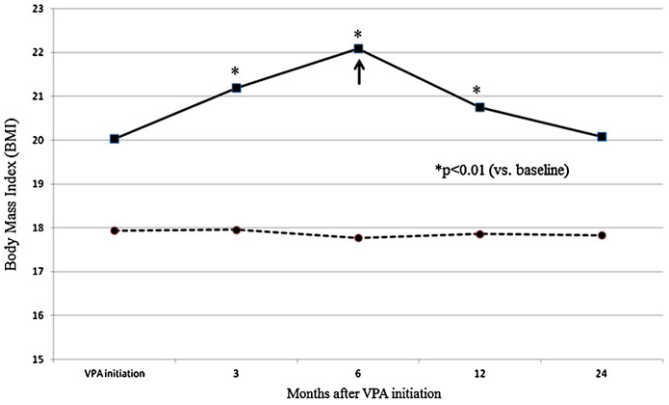

Fig. 2. Serial changes in the mean BMI. BMI in the weight gain group increased within 6 months after initiation of VPA treatment. However, the BMI decreased after 6 months. At the end of the study (year 2), an analysis of BMI revealed no significant change before initiation of treatment. By contrast, no obvious change was evident in the no weight gain group. Closed squares with solid lines indicate the weight gain group. Closed circles with dotted lines indicate the no weight gain group. Arrow indicates the onset of intensive behavior therapy.

No significant changes in mean carnitine concentrations were observed in any patients. No correlation was found between the carnitine concentrations, serum levels of VPA, and weight gain. Thyroid hormones, cholesterol, triglyceride levels, and liver enzymes remained unchanged in all patients.

4. Discussion

In this study, a significant increase in BMI was observed within 6 months after initiation of treatment in eight patients (53.3%). Furthermore, our results demonstrated that the occurrence of weight gain was more prevalent in females with epilepsy than in males. This is consistent with previous findings suggesting that VPA may induce weight gain in young women.[21] In some children, particularly adolescent girls, excessive weight gain has serious psychological effects. Some patients develop substantial weight gain on VPA, which can be treatment limiting.[22] The patients in our study did not develop substantial weight gain; however, this problem must be addressed if medication for females with epilepsy is begun before 20 years of age.

Various mechanisms have been proposed to explain the weight gain associated with VPA treatment. An increased consumption of food and energy-rich beverages because of an increased appetite and abnormal thirst has been suggested.[23,24] However, it appears that VPA has no effect on the total intake of calories.[25] In this study, all patients with marked weight gain reported an increased appetite. Thus, the factors contributing to weight gain during VPA therapy are not completely understood and there are likely to be multiple contributing factors, however, one factor may be

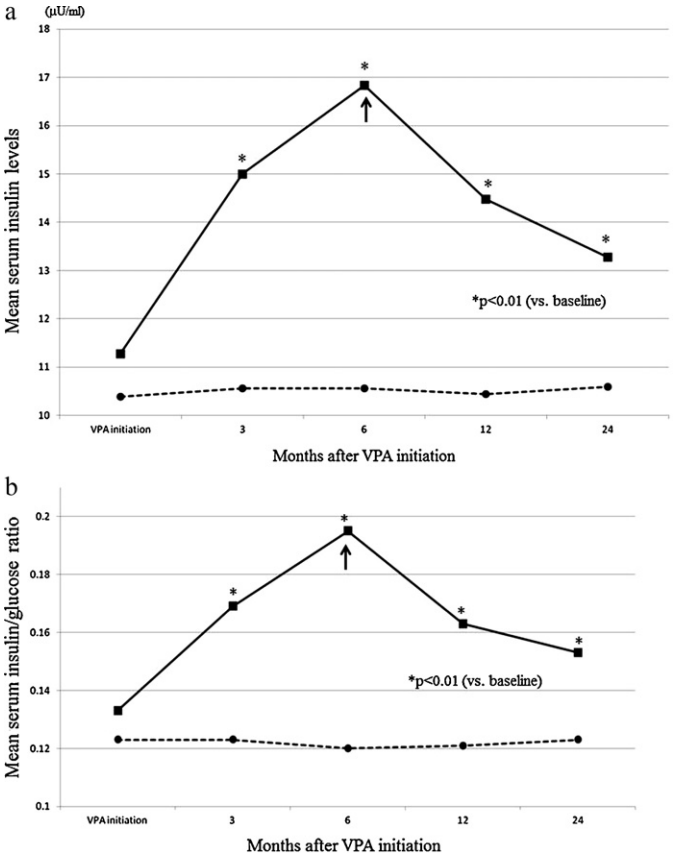

Fig. 3. Serial changes of mean serum insulin levels (a) and insulin/glucose ratio (b). Serum insulin levels and insulin/glucose ratio in the weight gain group increased within 6 months after initiation of VPA treatment. By contrast, no change was evident in the no weight gain group. Closed squares with solid lines indicate the weight gain group. Closed circles with dotted lines indicate the no weight gain group. Arrow indicates the onset of intensive behavior therapy.

increased appetite. In the patients with marked weight gain, increased insulin concentrations and insulin/glucose ratios were observed. Higher insulin and insulin/glucose levels may be involved in weight gain by stimulating appetite. On the other hand, in the patients without weight gain, who showed no increased appetite, no increase in serum insulin or insulin/glucose levels was demonstrated. These findings suggest that an increase in serum insulin and insulin/glucose levels may cause weight gain, possibly by stimulating appetite. The findings of decreased insulin levels within 2 months and body weight within 12 months suggest that hyperinsulinemia may play a primary role in VPA-induced metabolic changes.[26]

In our study, there were no significant reductions in glucose levels, consistent with a previous report.[7] The lack of a correlation between changes in insulin levels and glucose concentrations suggests the effect of additional factors. In the presence of palmoxirate, binding of VPA is decreased by a competitive mechanism.[27] Methyl palmoxirate inhibited insulin release evoked by several nutrient secretagogues.[28] Moreover, methyl palmoxirate also inhibited insulin release evoked by non-nutrient secretagogues.[29] These findings suggest the inhibitory action of methyl palmoxirate on insulin release may be attributable to a specific alteration of fatty acid oxidation rather than to an unexpected side-effect of the drug.[28] However, the study by Verrotti et al. revealed that abnormal glucose homeostasis was identified in 45% of patients.[30] They also reported that VPA causes metabolic syndrome in some patients, but not in all patients. In our study, there were no excessive weight gainers. Our results showed no significant changes in serum glucose levels and the lack of weight gain may be related to that. Further research is needed to clarify this point.

The results of the present study show these effects transiently without replacement of VPA. There is some evidence that exercise increases the long-term success rate, particularly if combined with behavioral modifications to alter lifestyle.[31] Any increase in physical activity is good, especially if accompanied by a decrease in sedentary activities such as watching television and playing computer games. We encouraged the patients to visit our office regularly. In addition, we explained the treatment plan clearly and the risks of adverse effects of drug therapy with VPA, including risks associated with irregular drug intake. Our study is prospective, and therefore anthropometric measures were available at specified points. These findings showed that successful weight management is possible for epileptic children with VPA-induced obesity without replacement of VPA or difficult diet restrictions.

Most patients find even modest weight gain unpleasant and development of obesity may in some cases make VPA unacceptable to the patient. However, it is not our intent to discourage the use of VPA. The results of the present study also show that in addition to VPA-related metabolic alterations, weight changes seem to be at least partially reversible by intense behavior therapy without discontinuation of medication. The study by Verrotti et al. has reported that metabolic syndrome is not caused by VPA medication but is due to the weight gain induced by VPA therapy.[30] Therefore, the preventive treatment for weight gain may be important. Our results are helpful to reassure children and their parents that weight gain will not persist. However, Verrotti et al. also have reported that feeding habits have apparently no effects on the development of metabolic syndrome.[30] Long-term weight loss and weight maintenance in children and adolescents can only be achieved if unhealthy eating and behavior are replaced with healthier lifestyle changes that persist into adulthood.[14] However, the results of child-directed treatments are disappointing in the long run.[32] They concluded that the habits of the parents have significant effects on child and parent BMI. The behavior therapy approach used in the present study did not recommend a calorie-restricted diet, but rather encouraged healthy eating habits for children and their families. This approach may have helped to encourage the children. The programed behavior therapy was introduced to the weight-gainers six months after initiation of VPA treatment. However, a preventive treatment may be needed before starting VPA therapy in high-risk patients. We have recommended the behavior therapy approach used in the present study from the beginning of VPA therapy in high-risk patients.

As our understanding of the anticonvulsant mechanisms of drugs like VPA increases, we should also try to learn more about the mechanisms causing adverse effects and how these can be prevented. Although the use of VPA is associated with weight gain, it may still be the best option for treating some specific epilepsy syndromes. Moreover, VPA is prescribed more frequently in patients with psychiatric disorders.[33] Concerns about potential weight gain should be discussed with patients before VPA therapy is begun and BMI should be monitored closely. These concerns should not preclude the use of VPA. Nevertheless, our findings of VPA-associated weight gain raise concerns about the use of VPA. Successful weight management with behavior therapy may be possible for epileptic children with VPA-induced obesity and without replacement of VPA.

Our sample of patients was small and therefore we cannot make definitive conclusions. Further research is necessary in this area with a larger sample of patients and a better determination of the intensity of behavior therapy that is needed.

5. Conclusions

These findings suggest that an increase in serum insulin and insulin/glucose levels may cause weight gain, possibly by stimulating appetite, and that weight changes may be reversible with behavior therapy without discontinuation of VPA.

Conflict of interest

None of the authors has any conflicts of interest to disclose.

Acknowledgments

This work was supported by Grants-in-Aid for Scientific Research (C) (22591124 and 22591123) and the Japan Epilepsy Research Foundation.

References

1. Yu P, Zhu G, Wu X, Li T, Xu L, Yue L, et al. A 6-month prospective study on efficacy safety and QOL profiles of extended-release formulation of valproate in patients with epilepsy. *Seizure* 2011;**20**:23–6.
2. Korkmazer N, Vurucu S, Demirkaya E, Unay B, Kul M, Akin R, et al. Serum and liver tissue biotinidase enzyme activity in rats which were administrated to valproic acid. *Brain and Development* 2006;**28**:515–20.
3. Viteri C, Codina M, Cobaleda S, Lahuerta J, Barriga J, Morales MD, for the Spanish QOLIE-10 Validation Study Group. Quality of life and treatment satisfaction in Spanish epilepsy patients on monotherapy with lamotrigine or valproic acid. *Seizure* 2010;**19**:432–8.
4. Corman CL, Leung NM, Guberman AH. Weight gain in epileptic patients during treatment with valproic acid: a retrospective study. *Canadian Journal of Neurological Sciences* 1997;**24**:240–4.
5. Vorum H, Gram L, Honore B. Valproate and palmitate binding to serum albumin in valproate-treated patients. Relation to obesity. *Epilepsy Research* 1993;**16**:55–64.
6. Sachs GS, Guille C. Weight gain associated with use of psychotropic medications. *Journal of Clinical Psychiatry* 1999;**60**(Suppl. 21):16–9.
7. Verrotti A, Scardapane A, Franzoni E, Manco R, Chiarelli F. Increased oxidative stress in epileptic children treated with valproic acid. *Epilepsy Research* 2008;**78**:171–7.
8. Biton V, Mirza W, Montouris G, Vuong A, Hammer AE, Barrett PS. Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy. *Neurology* 2001;**56**:172–7.
9. Faught E, Limdi NA. Adverse and beneficial side effects of antiepileptic drugs. In: Ettinger AB, Devinsky O, editors. *Managing epilepsy and co-existing disorders*. Woburn: Butterworth-Heinemann; 2002. p. 447–64.
10. Isojarvi JIT, Laatikainen TJ, Knip M, Pakarinen AJ, Juntunen KTS, Myllyla VV. Obesity and endocrine disorders in women taking valproate for epilepsy. *Annals of Neurology* 1996;**39**:579–84.
11. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health Report for the International Obesity Task Force Childhood Obesity Working Group. *Obesity Reviews* 2004;**5**:4–104.
12. Zimmet P, Alberti G, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents. *Lancet* 2007;**369**:2059–61.
13. Duffy G, Spence SH. The effectiveness of cognitive self-management as an adjunct to a behavioural intervention for childhood obesity: a research note. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 1993;**34**:1043–50.
14. Epstein LH, Myers MD, Raynor HA, Saelens BE. Treatment of pediatric obesity. *Pediatrics* 1998;**101**:554–70.
15. Braet C, Van Winckel M, Van Leeuwen K. Follow-up results of different treatment programs for obese children. *Acta Paediatrica* 1997;**86**:397–402.
16. Van Dorsten B, Lindley EM. Cognitive and behavioral approaches in the treatment of obesity. *Medical Clinics of North America* 2011;**95**:971–88.
17. Annesi JJ. Self-regulatory skills usage strengthens the relations of self-efficacy for improved eating, exercise, and weight in the severely obese: toward an explanatory model. *Behavioral Medicine* 2011;**37**:71–6.
18. Arroyo S. Valproate. In: Shorvon S, Perucca E, Fish D, Dodson E, editors. *The treatment of epilepsy*. 2nd ed. Massachusetts: Blackwell Science Ltd.; 1996. p. 528–39.
19. Nakane T, Asayama K, Hayashibe H, Uchida N, Kodera K, Dobashi K. Changes in serum leptin concentration during behavioral therapy in obese children. *Endocrine Journal* 1999;**46**:703–9.
20. Asayama K, Uchida N, Hayashibe H, Dobashi K, Nakane T, Kodera K, et al. A new mode of therapy for obese children in Japan. *International Journal of Obesity* 1998;**22**(Suppl. 3):S62.
21. Wirrell EC. Valproic acid-associated weight gain in older children and teens with epilepsy. *Pediatric Neurology* 2003;**28**:126–9.
22. Beydoun AA, Farrell K, Nasreddine WM. Valproate. In: Engel Jr J, Pedley TA, editors. *Epilepsy. A comprehensive text book*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 1673–82.
23. Egger J, Bret EM. Effects of sodium valproate in 100 children with special reference to weight. *British Medical Journal (Clinical Research)* 1981;**283**:577–81.
24. Convanis A, Gupta K, Jeavons PM. Sodium valproate: monotherapy and polytherapy. *Epilepsia* 1982;**23**:693–720.
25. Breum L, Astrup A, Gram L, Andersen T, Stokholm KH, Christensen NJ, et al. Metabolic changes during treatment with valproate in humans: implication for untoward weight gain. *Metabolism Clinical and Experimental* 1992;**41**:666–70.
26. Isojarvi JI, Rattya J, Myllyla VV, Knip M, Koivunen R, Pakarinen AJ, et al. Valproate, lamotorigine and insulin-mediated risks in women with epilepsy. *Annals of Neurology* 1998;**43**:446–51.
27. Brodersen R, Jorgensen N, Vorum H, Krukow N. Valproate and palmitate binding to human serum albumin: a hypothesis on obesity. *Molecular Pharmacology* 1990;**37**:704–9.
28. Malaisse WJ, Malaisse-Lagae F, Sener A, Hellerstrom C. Participation of endogenous fatty acids in the secretory activity of the pancreatic B-cell. *Biochemical Journal* 1985;**227**:995–1002.
29. Malaisse WJ, Lebrun P, Herchuelz A, Sener A, Malaisse-Lagae F. Synergistic effect of a tumor-promoting phorbol ester and a hypoglycemic sulfonylurea upon insulin release. *Endocrinology* 1983;**113**:1870–7.
30. Verrotti A, Manco R, Agostinelli S, Coppola G, Chiarelli F. The metabolic syndrome in overweight epileptic patients treated with valproic acid. *Epilepsia* 2010;**51**:268–73.
31. Harris MB, Hallbauer ES. Self-directed weight control through eating and exercise. *Behaviour Research and Therapy* 1973;**11**:523–9.
32. Jansen E, Mulkens S, Jansen A. Tackling childhood overweight: treating parents exclusively is effective. *International Journal of Obesity* 2011;**35**:501–9.
33. Kaufman KR. Antiepileptic drugs in the treatment of psychiatric disorders. *Epilepsy Behavior* 2011;**21**:1–11.